PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 491/22, A61K 31/435 // (C07D 491/22, 311:00, 221:00, 221:00, 209:00) (C07D 491/22, 317:00, 311:00, 221:00, 221:00, 209:00)

A1

(11) International Publication Number: **WO 96/37496**

(43) International Publication Date: 28 November 1996 (28.11.96)

(21) International Application Number: PCT/EP96/02008

(22) International Filing Date: 10 May 1996 (10.05.96)

(30) Priority Data:
9510716.5 26 May 1995 (26.05.95) GB

(71) Applicant *(for all designated States except US)*: PHARMACIA S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

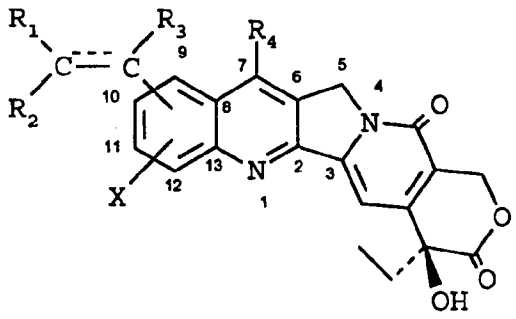
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CABRI, Walter [IT/IT]; Via Massimo d'Azeglio, 29, I-20089 Rozzano (IT). CANDIANI, Ilaria [IT/IT]; Via del Chisso, 5, I-21052 Busto Arsizio (IT). BEDESCHI, Angelo [IT/IT]; Via Pietro Redaelli, 11, I-20146 Milano (IT). ZARINI, Franco [IT/IT]; Via Giuseppe di Vittorio, 41, I-20019 Settimo Milanese (IT). PENCO, Sergio [IT/IT]; Via Milly Mignone, 5, I-20153 Milano (IT).

(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, JP, KR, KZ, MX, NO, NZ, PL, RU, SG, SI, UA, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBSTITUTED CAMPTOTHECIN DERIVATIVES AND PROCESS FOR THEIR PREPARATION

(57) Abstract



(I)

The present invention relates to substituted camptothecin derivatives of formula (I) wherein the symbol ---- represents a single or double bond; R_1, R_2 and R_3 are as defined under (a) or (b) below: (a) R_1 and R_2 are, each independently, hydrogen; C_1-C_4 alkyl; C_3-C_7 cycloalkyl; phenyl C_1-C_6 alkyl; an optionally substituted phenyl ring; $-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen, C_1-C_6 alkyl or benzyl and the other is hydrogen, C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted phenoxycarbonyl or phenyl C_1-C_6 alkoxycarbonyl, or R_5 and R_6, combined together with the nitrogen atom to which they are linked, form a 4-7 membered saturated, optionally substituted, heteromonocyclic ring residue; $COOR_8$ wherein R_8 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; or COR_9 wherein Rg is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_6 alkyl, an optionally substituted phenyl ring or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are, each independently, hydrogen or C_1-C_6 alkyl; and R_3 is hydrogen, C_1-C_6 alkyl or an optionally substituted phenyl ring; or (b) R_1 and R_3, combined together, form a 5-8 membered, optionally substituted, carbomonocyclic ring; and R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_7 cycloalkyl; R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; X is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkanoyloxy, benzoyloxy, amino, hydroxy, nitro, halogen or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, and the pharmaceutically acceptable salts thereof. The compounds according to the invention are useful in therapy as antitumor agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

SUBSTITUTED CAMPTOTHECIN DERIVATIVES AND PROCESS FOR THEIR PREPARATION

The present invention relates to new substituted camptothecin derivatives possessing antitumor activity, to a process for their preparation, and to pharmaceutical compositions containing them.

Background of the invention

Camptothecin and some of its analogs display potent antitumor activity by the inhibition of Topoisomerase I, that is an enzyme involved in some important cellular functions and cellular growth (see, for instance, Wani et al., J. Med. Chem. 1987, 30, 1774; Hsiang et al., Cancer Res. 1989, 49, 4385; Cancer Res. 1989, 49, 1465).

Anticancer activity of Camptothecin both in vitro and in vivo is significantly greater for the lactone versus the carboxylate form (as disclosed, for instance, by W.J. Slichenmyer et al., in "The Current Status of Camptothecin Analogues as Antitumor Agents", J. Natl. Cancer Inst. 1993, 85, 271-291, and reference therein), since a closed a-hydroxy lactone ring is an important structural requirement for both passive diffusion of drug into cancer cells, as well as for successful drug interaction with the pharmacological target.

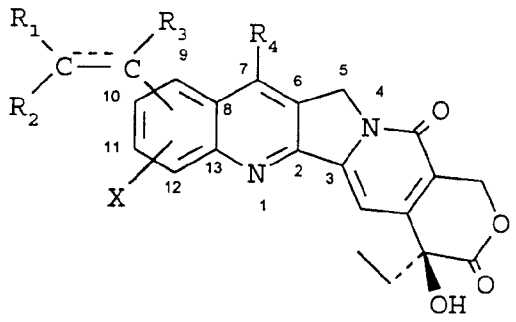
It has recently been pointed out that, in the presence of biologically relevant levels of human albumin, the biologically active form of camptothecin has a very short half-life (about 12 min.), and 2 hours after drug addition to human plasma, a percentage greater than 99% of the drug has converted to camptothecin carboxylate, the biologically inactive and potentially toxic form of the drug (see Burke, G.T.; Mi, Z. "The Structural Basis of Camptothecin

Interactions with Human Serum Albumin: Impact on Drug Stability", J. Med. Chem. 1994, 37, 40-46). The same authors disclose also the importance of the substitution in 9 and 7 positions on the camptothecin nucleus in order to improve drug stability in the presence of albumin.

There is therefore a need to find new camptothecin derivatives that have high intrinsic potency, and may gain, at the same time, stability in the presence of serum albumin.

Description of the invention

Accordingly, the present invention relates to substituted camptothecin derivatives of formula (I)



(I)

wherein

the symbol ---- represents a single or double bond;

R_1, R_2 and R_3 are as defined under (a) or (b) below:

(a) R_1 and R_2 are, each independently,

hydrogen;

C_1-C_4 alkyl;

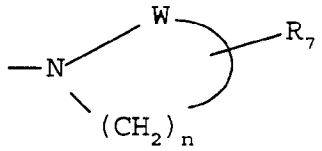
C_3-C_7 cycloalkyl;

phenyl C_1-C_6 alkyl;

an optionally substituted phenyl ring;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen, C_1-C_6 alkyl or benzyl and the other is hydrogen C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, an optionally substituted phenoxycarbonyl or phenyl C_1-C_6

alkoxycarbonyl, or R_5 and R_6, combined together with the nitrogen atom to which they are linked, form a 4-7 membered saturated, optionally substituted, heteromonocyclic ring residue, represented by a group (G)



(G)

wherein W is -C=O, R_7 is hydrogen or C_1-C_6 alkyl and n is an integer of 2 to 5;

$COOR_8$ wherein R_8 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_6 alkyl, an optionally substituted phenyl ring or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are, each independently, hydrogen or C_1-C_6 alkyl; and

R_3 is hydrogen, C_1-C_6 alkyl or an optionally substituted phenyl ring; or

(b) R_1 and R_3, combined together, form a 5-8 membered, optionally substituted, carbomonocyclic ring; and

R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_7 cycloalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl;

X is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkanoyloxy, benzoyloxy, amino, hydroxy, nitro, halogen or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, and the pharmaceutically acceptable salts thereof.

In the formulae of the present specification, a dotted line (---) indicates a substituent below the plane of the ring; a wedged line (◄) indicates a substituent above the plane of the ring.

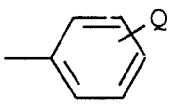
When in a compound of formula (I) the symbol ---- means a double bond, both Z and E isomers and a mixture of Z and E isomers are included into the scope of the present invention.

Pharmaceutically acceptable salts according the invention are the salts with pharmaceutically acceptable acids, both inorganic acids such as, e.g. hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic or nitric acid, and organic acids such as, e.g., citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulfonic, ethanesulfonic, benzenesulfonic, or p-toluensulfonic acid.

Pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic, i.e. carboxy, group with pharmaceutically acceptable bases are also included in the scope of the present invention.

Pharmaceutically acceptable bases may be both inorganic bases such as, for instance, alkali metal, e.g. sodium or potassium, or alkaline earth metal, e.g. calcium or magnesium, hydroxides, and organic bases such as, for instance, alkyl amines, e.g. methylamine or triethylamine, aralkylamines, e.g. benzylamine, dibenzylamine, a- or b-phenyl-ethylamine, or heterocyclic amines such as, e.g., piperidine, 1-methyl-piperidine, piperazine or morpholine.

An optionally substituted phenyl ring may be represented by a group



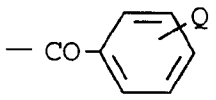
wherein

Q, linked to the ortho, meta or para position of the phenyl ring, represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyloxy, nitro or halogen.

Preferably Q is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen.

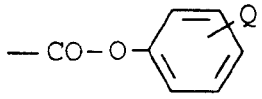
Particularly preferred values of Q are hydrogen, methoxy and chlorine.

An optionally substituted benzoyl may be represented by a group



wherein Q is as defined above.

An optionally substituted phenoxycarbonyl may be represented by a group



wherein Q is as defined above.

A 5-8 membered, optionally substituted carbomonocyclic ring is, when the symbol ---- is used to denote a single bond, for example cyclopentyl or cyclohexyl, or, when the symbol ---- is used to denote a double bond, cyclopenten-1-yl or cyclohexen-1-yl.

In the present specification, the hydrocarbon chain of the alkyl, alkoxy, alkanoyl, alkanoyloxy and alkoxycarbonyl groups may be a straight or branched chain.

Preferably, C_1-C_6 alkyl is C_1-C_4 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or t-butyl.

Preferably, C_1-C_4 alkyl is methyl, ethyl or propyl.

Preferably, C_3-C_7 cycloalkyl is C_4-C_6 cycloalkyl, e.g. cyclobutyl, cyclopentyl or cyclohexyl.

Preferably, C_1-C_6 alkoxy is C_1-C_4 alkoxy, e.g. methoxy, ethoxy or propoxy.

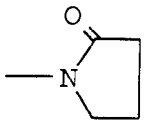
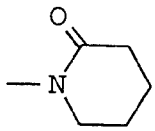
Preferably, C_1-C_6 alkanoyl is C_1-C_4 alkanoyl, e.g. methanoyl, ethanoyl or propanoyl.

Preferably, C_1-C_6 alkanoyloxy is C_1-C_4 alkanoyloxy, e.g. methanoyloxy, ethanoyloxy or propanoyloxy.

Preferably, C_1-C_6 alkoxycarbonyl is C_1-C_4 alkoxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or isopropoxicarbonyl.

Preferably, an optionally substituted C_1-C_6 alkoxycarbonyl is trichloroethoxycarbonyl.

Preferred meanings of the heteromonocyclic ring residue represented by the above defined group (G) are


and


A preferred class of compounds according to this invention is represented by compounds of the above formula (I) wherein the symbol ---- represents a single or double bond; R_1 and R_2 are, each independently, hydrogen;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen and the other is hydrogen, C_1-C_6 alkanoyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenoxy-carbonyl or phenyl C_1-C_6 alkoxycarbonyl;

$COOR_8$ wherein R_8 is hydrogen or C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, unsubstituted phenyl or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are both hydrogen;

R_3 is hydrogen;

R_4 is hydrogen or C_1-C_6 alkyl;

X is hydrogen, hydroxy, amino, C_1-C_6 alkoxy or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, and the pharmaceutically acceptable salts thereof.

Examples of specific compounds preferred under the invention are the following:

9-vinyl camptothecin (1);

(E)-9-(2-methoxycarbonyl-ethenyl)camptothecin (2);

9-(2-hydroxycarbonyl-ethenyl)camptothecin (3);

(Z)-9-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (4);

9-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (5);

9-(3-oxo-but-1-enyl)camptothecin (6);

9-(3-oxo-3-phenyl-propenyl)camptothecin (7);

9-(2-aminocarbonyl-ethenyl)camptothecin (8);

7-ethyl-9-vinyl camptothecin (9);

7-ethyl-9-(2-methoxycarbonyl-ethenyl)camptothecin (10);

7-ethyl-9-(2-hydroxycarbonyl-ethenyl)camptothecin (11);

7-ethyl-9-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (12);

7-ethyl-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (13);

7-ethyl-9-(3-oxo-but-1-enyl)camptothecin (14);

7-ethyl-9-(3-oxo-3-phenyl-propenyl)camptothecin (15);

7-ethyl-9-(2-aminocarbonyl-ethenyl)camptothecin (16);

10-vinyl camptothecin (17);

(E)-10-(2-methoxycarbonyl-ethenyl)camptothecin (18);

10-(2-hydroxycarbonyl-ethenyl)camptothecin (19);

10-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (20);

10-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (21);

10-(3-oxo-but-1-enyl)camptothecin (22);

10-(3-oxo-3-phenyl-propenyl)camptothecin (23);

10-(2-aminocarbonyl-ethenyl)camptothecin (24);

7-ethyl-10-vinyl camptothecin (25);

7-ethyl-10-(2-methoxycarbonyl-ethenyl)camptothecin (26);

7-ethyl-10-(2-hydroxycarbonyl-ethenyl)camptothecin (27);

7-ethyl-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (28);

7-ethyl-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (29);

7-ethyl-10-(3-oxo-but-1-enyl)camptothecin (30);

7-ethyl-10-(3-oxo-3-phenyl-propenyl)camptothecin (31);

7-ethyl-10-(2-aminocarbonyl-ethenyl)camptothecin (32);

10-hydroxy-9-vinyl camptothecin (33);

10-hydroxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (34);

10-hydroxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (35);

10-hydroxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (36);

10-hydroxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (37);

10-hydroxy-9-(3-oxo-but-1-enyl)camptothecin (38);

10-hydroxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (39);

10-hydroxy-9-(2-aminocarbonyl-ethenyl)camptothecin (40);

10,11-methylendioxy-9-vinyl camptothecin (41);

10,11-methylendioxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (42);

10,11-methylendioxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (43);

10,11-methylendioxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (44);

10,11-methylendioxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (45);

10,11-methylendioxy-9-(3-oxo-but-1-enyl)camptothecin (46);

10,11-methylendioxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (47);

10,11-methylendioxy-9-(2-aminocarbonyl-ethenyl)camptothecin (48);

10-methoxy-9-vinyl camptothecin (49);

10-methoxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (50);

10-methoxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (51);

10-methoxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (52);

10-methoxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (53);

10-methoxy-9-(3-oxo-but-1-enyl)camptothecin (54);

10-methoxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (55);
10-methoxy-9-(2-aminocarbonyl-ethenyl)camptothecin (56);
11-vinyl camptothecin (57);
11-(2-methoxycarbonyl-ethenyl)camptothecin (58);
11-(2-hydroxycarbonyl-ethenyl)camptothecin (59);
11-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (60);
11-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (61);
11-(3-oxo-but-1-enyl)camptothecin (62);
11-(3-oxo-3-phenyl-propenyl)camptothecin (63);
11-(2-aminocarbonyl-ethenyl)camptothecin (64);
12-vinyl camptothecin (65);
(E)-12-(2-methoxycarbonyl-ethenyl)camptothecin (66);
12-(2-hydroxycarbonyl-ethenyl)camptothecin (67);
(Z)-12-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (68);
12-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (69);
12-(3-oxo-but-1-enyl)camptothecin (70);
12-(3-oxo-3-phenyl-propenyl)camptothecin (71);
12-(2-aminocarbonyl-ethenyl)camptothecin (72);
9-amino-10-vinyl camptothecin (73);
9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (74);
9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (75);
9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (76);
9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (77);
9-amino-10-(3-oxo-but-1-enyl)camptothecin (78);
9-amino-10-(3-oxo-3-phenyl-propenyl)camptothecin (79);
9-amino-10-(2-aminocarbonyl-ethenyl)camptothecin (80);
7-ethyl-9-amino-10-vinyl camptothecin (81);
7-ethyl-9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (82);

7-ethyl-9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (83);

7-ethyl-9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (84);

7-ethyl-9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (85);

7-ethyl-9-amino-10-(3-oxo-but-1-enyl)camptothecin (86);

7-ethyl-9-amino-10-(3-oxo-3-phenyl-propenyl)camptothecin (87);

7-ethyl-9-amino-10-(2-aminocarbonyl-ethenyl)camptothecin (88);

9-ethyl camptothecin (1');

9-(2-methoxycarbonyl-ethyl)camptothecin (2');

9-(2-hydroxycarbonyl-ethyl)camptothecin (3');

9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (4');

9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (5');

9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (6');

9-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (7');

9-(3-oxo-butyl)camptothecin (8');

9-(3-oxo-3-phenyl-propyl)camptothecin (9');

9-(2-aminocarbonyl-ethyl)camptothecin (10');

7-ethyl-9-ethyl camptothecin (11');

7-ethyl-9-(2-methoxycarbonyl-ethyl)camptothecin (12');

7-ethyl-9-(2-hydroxycarbonyl-ethyl)camptothecin (13');

7-ethyl-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (14');

7-ethyl-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (15');

7-ethyl-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (16');

7-ethyl-9-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (17');

7-ethyl-9-(3-oxo-butyl)camptothecin (18');

7-ethyl-9-(3-oxo-3-phenyl-propyl)camptothecin (19');

7-ethyl-9-(2-aminocarbonyl ethyl)camptothecin (20');
10-ethyl camptothecin (21');
10-(2-methoxycarbonyl-ethyl)camptothecin (22');
10-(2-hydroxycarbonyl-ethyl)camptothecin (23');
10-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (24');
10-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (25');
10-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (26');
10-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (27');
10-(3-oxo-butyl)camptothecin (28');
10-(3-oxo-3-phenyl-propyl)camptothecin (29');
10-(2-aminocarbonyl-ethyl)camptothecin (30');
7-ethyl-10-ethyl camptothecin (31');
7-ethyl-10-(2-methoxycarbonyl-ethyl)camptothecin (32');
7-ethyl-10-(2-hydroxycarbonyl-ethyl)camptothecin (33');
7-ethyl-10-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (34');
7-ethyl-10-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin 35');
7-ethyl-10-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin 36');
7-ethyl-10-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (37');
7-ethyl-10-(3-oxo-butyl)camptothecin (38');
7-ethyl-10-(3-oxo-3-phenyl-propyl)camptothecin (39');
7-ethyl-10-(2-aminocarbonyl-ethyl)camptothecin (40');
11-ethyl camptothecin (41');
11-(2-methoxycarbonyl-ethyl)camptothecin (42');
11-(2-hydroxycarbonyl-ethyl)camptothecin (43');
11-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (44');
11-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (45');

11-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (46');
11-[(2-acetylamino-2-hydroxycarbonyl)-ethyl]camptothecin (47');
11-(3-oxo-butyl)camptothecin (48');
11-(3-oxo-3-phenyl-propyl)camptothecin (49');
11-(2-aminocarbonyl-ethyl)camptothecin (50');
9-amino-12-ethyl camptothecin (51');
9-amino-12-(2-methoxycarbonyl-ethyl)camptothecin (52');
9-amino-12-(2-hydroxycarbonyl-ethyl)camptothecin (53');
9-amino-12-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (54');
9-amino-12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin 55');
9-amino-12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin 56');
9-amino-12-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (57');
9-amino-12-(3-oxo-butyl)camptothecin (58');
9-amino-12-(3-oxo-3-phenyl-propyl)camptothecin (59');
9-amino-12-(2-aminocarbonyl-ethyl)camptothecin (60');
10-amino-9-ethyl camptothecin (61');
10-amino-9-(2-methoxycarbonyl-ethyl)camptothecin (62');
10-amino-9-(2-hydroxycarbonyl-ethyl)camptothecin (63');
10-amino-9-[(2-acetylamino-2-methoxycarbonyl)-ethyl] camptothecin (64');
10-amino-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (65');
10-amino-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (66');
10-amino-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (67');
10-amino-9-(3-oxo-butyl)camptothecin (68');

10-amino-9-(3-oxo-3-phenyl-3-one-propyl)camptothecin (69');
10-amino-9-(2-aminocarbonyl-ethyl)camptothecin (70');
12-ethyl camptothecin (71');
12-(2-methoxycarbonyl-ethyl)camptothecin (72');
12-(2-hydroxycarbonyl-ethyl)camptothecin (73');
12-[(2R,S,)(2-acetylamino-2-methoxycarbonyl)-ethyl]camptothecin (74');
12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (75');
12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (76');
12-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (77');
12-(3-oxo-butyl)camptothecin (78');
12-(3-oxo-3-phenyl-propyl)camptothecin (79');
12-(2-aminocarbonyl-ethyl)camptothecin (80');
10-hydroxy-9-ethyl camptothecin (81');
10-hydroxy-9-(2-methoxycarbonyl-ethyl)camptothecin (82');
10-hydroxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (83');
10-hydroxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (84');
10-hydroxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (85');
10-hydroxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (86');
10-hydroxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (87');
10-hydroxy-9-(3-oxo-butyl)camptothecin (88');
10-hydroxy-9-(3-oxo-3-phenyl-3-one-propyl)camptothecin (89');
10-hydroxy-9-(2-aminocarbonyl-ethyl)camptothecin (90');
10,11-methylendioxy-9-ethyl camptothecin (91');
10,11-methylendioxy-9-(2-methoxycarbonyl-ethyl)camptothecin (92');
10,11-methylendioxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (93');

10,11-methylendioxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (94');

10,11-methylendioxy-9-[(2-amino-2-methoxycarbonyl]-ethyl) camptothecin (95');

10,11-methylendioxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (96');

10,11-methylendioxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (97');

10,11-methylendioxy-9-(3-oxo-butyl)camptothecin (98');

10,11-methylendioxy-9-(3-oxo-3-phenyl-propyl)camptothecin (99');

10,11-methylendioxy-9-(2-aminocarbonyl-ethyl)camptothecin (100');

10-methoxy-9-ethyl camptothecin (101');

10-methoxy-9-(2-methoxycarbonyl-ethyl)camptothecin (102');

10-methoxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (103');

10-methoxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (104');

10-methoxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (105');

10-methoxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (106');

10-methoxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (107');

10-methoxy-9-(3-oxo-butyl)camptothecin (108');

10-methoxy-9-(3-oxo-3-phenyl-propyl)camptothecin (109');

10-methoxy-9-(2-aminocarbonyl-ethyl)camptothecin (110');

and, where a salifiable substituent is present on the molecule framework, their pharmaceutically acceptable salts.

The structural formula of the above listed compounds is illustrated in the following Table 1 with reference to the above formula (I) wherein the symbol ---- represents a double

bond, and Table 2 with reference to the above formula (I) wherein the symbol ---- represents a single bond.

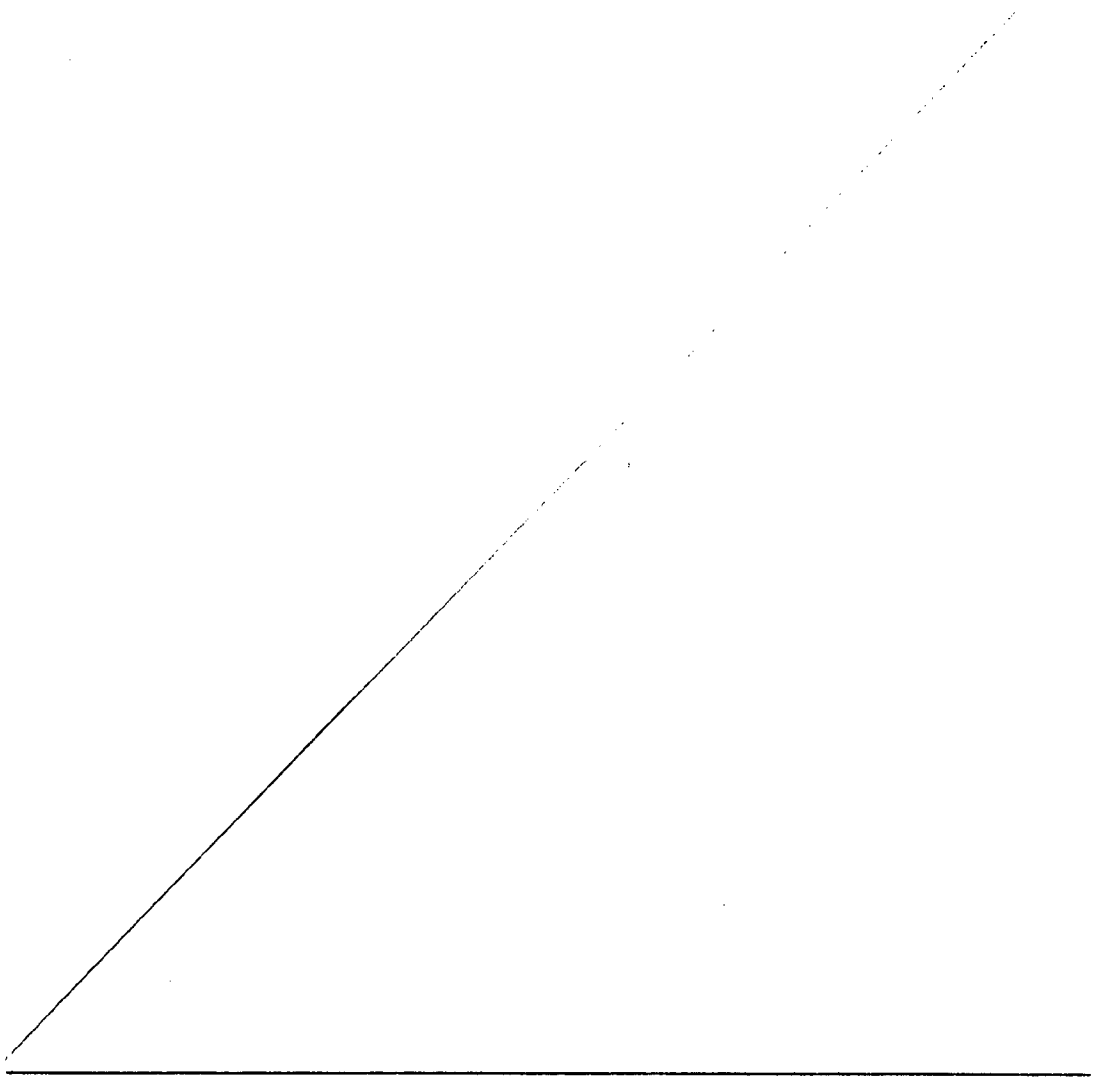


Table 1

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
1	$-CH=CH_2$	-	-	-	-	H	H
2	$-CH=CH-COOR_8$	-	-	CH_3	-	H	H
3	$-CH=CH-COOR_8$	-	-	H	-	H	H
4	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
5	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	H
6	$-CH=CH-COR_9$	-	-	-	CH_3	H	H
7	$-CH=CH-COR_9$	-	-	-	Ph	H	H
8	$-CH=CH-COR_9$	-	-	-	NH_2	H	H
9	$-CH=CH_2$	-	-	-	-	Et	H
10	$-CH=CH-COOR_8$	-	-	CH_3	-	Et	H
11	$-CH=CH-COOR_8$	-	-	H	-	Et	H
12	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	Et	H
13	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	Et	H
14	$-CH=CH-COR_9$	-	-	-	CH_3	Et	H
15	$-CH=CH-COR_9$	-	-	-	Ph	Et	H
16	$-CH=CH-COR_9$	-	-	-	NH_2	Et	H
Compound	10-substituent	R_5	R_6	R_8	R_9	R_4	X
17	$-CH=CH_2$	-	-	-	-	H	H
18	$-CH=CH-COOR_8$	-	-	CH_3	-	H	H
19	$-CH=CH-COOR_8$	-	-	H	-	H	H
20	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
21	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	H
22	$-CH=CH-COR_9$	-	-	-	CH_3	H	H
23	$-CH=CH-COR_9$	-	-	-	Ph	H	H
24	$-CH=CH-COR_9$	-	-	-	NH_2	H	H

Table 1 (continued)

Compound	10-substituent	R_5	R_6	R_8	R_9	R_4	X
25	$-CH=CH_2$	-	-	-	-	Et	H
26	$-CH=CH-COOR_8$	-	-	CH_3	-	Et	H
27	$-CH=CH-COOR_8$	-	-	H	-	Et	H
28	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	Et	H
29	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	Et	H
30	$-CH=CH-COR_9$	-	-	-	CH_3	Et	H
31	$-CH=CH-COR_9$	-	-	-	Ph	Et	H
32	$-CH=CH-COR_9$	-	-	-	NH_2	Et	H
Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
33	$-CH=CH_2$	-	-	-	-	H	10-OH
34	$-CH=CH-COOR_8$	-	-	CH_3	-	H	10-OH
35	$-CH=CH-COOR_8$	-	-	H	-	H	10-OH
36	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	10-OH
37	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	10-OH
38	$-CH=CH-COR_9$	-	-	-	CH_3	H	10-OH
39	$-CH=CH-COR_9$	-	-	-	Ph	H	10-OH
40	$-CH=CH-COR_9$	-	-	-	NH_2	H	10-OH
41	$-CH=CH_2$	-	-	-	-	H	10,11-OCH_2O-
42	$-CH=CH-COOR_8$	-	-	CH_3	-	H	10,11-OCH_2O-
43	$-CH=CH-COOR_8$	-	-	H	-	H	10,11-OCH_2O-
44	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	10,11-OCH_2O-
45	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	10,11-OCH_2O-
46	$-CH=CH-COR_9$	-	-	-	CH_3	H	10,11-OCH_2O-
47	$-CH=CH-COR_9$	-	-	-	Ph	H	10,11-OCH_2O-
48	$-CH=CH-COR_9$	-	-	-	NH_2	H	10,11-OCH_2O-

Table 1 (continued)

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
49	$-CH=CH_2$	-	-	-	-	H	10-OCH_3
50	$-CH=CH-COOR_8$	-	-	CH_3	-	H	10-OCH_3
51	$-CH=CH-COOR_8$	-	-	H	-	H	10-OCH_3
52	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	10-OCH_3
53	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	10-OCH_3
54	$-CH=CH-COR_9$	-	-	-	CH_3	H	10-OCH_3
55	$-CH=CH-COR_9$	-	-	-	Ph	H	10-OCH_3
56	$-CH=CH-COR_9$	-	-	-	NH_2	H	10-OCH_3
Compound	11-substituted	R_5	R_6	R_8	R_9	R_4	X
57	$-CH=CH_2$	-	-	-	-	H	H
58	$-CH=CH-COOR_8$	-	-	CH_3	-	H	H
59	$-CH=CH-COOR_8$	-	-	H	-	H	H
60	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
61	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	H
62	$-CH=CH-COR_9$	-	-	-	CH_3	H	H
63	$-CH=CH-COR_9$	-	-	-	Ph	H	H
64	$-CH=CH-COR_9$	-	-	-	NH_2	H	H

Table 1 (continued)

Compound	12-substituent	R_5	R_6	R_8	R_9	R_4	X
65	$-CH=CH_2$	-	-	-	-	H	H
66	$-CH=CH-COOR_8$	-	-	CH_3	-	H	H
67	$-CH=CH-COOR_8$	-	-	H	-	H	H
68	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
69	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	H
70	$-CH=CH-COR_9$	-	-	-	CH_3	H	H
71	$-CH=CH-COR_9$	-	-	-	Ph	H	H
72	$-CH=CH-COR_9$	-	-	-	NH_2	H	H
Compound	10-substituent	R_5	R_6	R_8	R_9	R	X
73	$-CH=CH_2$	-	-	-	-	H	9-NH_2
74	$-CH=CH-COOR_8$	-	-	CH_3	-	H	9-NH_2
75	$-CH=CH-COOR_8$	-	-	H	-	H	9-NH_2
76	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	H	9-NH_2
77	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	H	9-NH_2
78	$-CH=CH-COR_9$	-	-	-	CH_3	H	9-NH_2
79	$-CH=CH-COR_9$	-	-	-	Ph	H	9-NH_2
80	$-CH=CH-COR_9$	-	-	-	NH_2	H	9-NH_2
81	$-CH=CH_2$	-	-	-	-	Et	9-NH_2
82	$-CH=CH-COOR_8$	-	-	CH_3	-	Et	9-NH_2
83	$-CH=CH-COOR_8$	-	-	H	-	Et	9-NH_2
84	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	CH_3	-	Et	9-NH_2
85	$-CH=\underset{\underset{NR_5R_6}{\vert}}{C}-COOR_8$	H	$COCH_3$	H	-	Et	9-NH_2
86	$-CH=CH-COR_9$	-	-	-	CH_3	Et	9-NH_2
87	$-CH=CH-COR_9$	-	-	-	Ph	Et	9-NH_2
88	$-CH=CH-COR_9$	-	-	-	NH_2	Et	9-NH_2

Table 2

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
1'	$-CH_2-CH_3$	-	-	-	-	H	H
2'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	H
3'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	H
4'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
5'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	H
6'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	H
7'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	H
8'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	H
9'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	H
10'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	H
11'	$-CH_2-CH_3$	-	-	-	-	Et	H
12'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	Et	H
13'	$-(CH_2)_2-COOR_8$	-	-	H	-	Et	H
14'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	Et	H
15'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	Et	H
16'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	Et	H
17'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	Et	H
18'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	Et	H
19'	$-(CH_2)_2-COR_9$	-	-	-	Ph	Et	H
20'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	Et	H

Table 2 (continued)

Compound	10-substituent	R_5	R_6	R_8	R_9	R_4	X
21'	$-CH_2-CH_3$	-	-	-	-	H	H
22'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	H
23'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	H
24'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
25'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	H
26'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	H
27'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	H
28'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	H
29'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	H
30'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	H
31'	$-CH_2-CH_3$	-	-	-	-	Et	H
32'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	Et	H
33'	$-(CH_2)_2-COOR_8$	-	-	H	-	Et	H
34'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	Et	H
35'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	Et	H
36'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	Et	H
37'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	Et	H
38'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	Et	H
39'	$-(CH_2)_2-COR_9$	-	-	-	Ph	Et	H
40'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	Et	H

Table 2 (continued)

Compound	11-substituent	R_5	R_6	R_8	R_9	R_4	X
41'	$-CH_2-CH_3$	-	-	-	-	H	H
42'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	H
43'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	H
44'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	H
45'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	H
46'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	H
47'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	H
48'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	H
49'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	H
50'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	H
Compound	12-substituent	R_5	R_6	R_8	R_9	R_4	X
51'	$-CH_2-CH_3$	-	-	-	-	H	9-NH_2
52'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	9-NH_2
53'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	9-NH_2
54'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	9-NH_2
55'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	9-NH_2
56'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	9-NH_2
57'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	9-NH_2
58'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	9-NH_2
59'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	9-NH_2
60'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	9-NH_2

Table 2 (continued)

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
61'	$-CH_2-CH_3$	-	-	-	-	H	10-NH_2
62'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	10-NH_2
63'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	10-NH_2
64'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	10-NH_2
65'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	10-NH_2
66'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	10-NH_2
67'	$-CH_2-CH(NR_5R_6)-COOR_8$	H	$COCH_3$	H	-	H	10-NH_2
68'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	10-NH_2
69'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	10-NH_2
70'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	10-NH_2
Compound	12-substituent	R_5	R_6	R_8	R_9	R_4	X
71'	$-CH_2-CH_3$	-	-	-	-	H	H
72'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	H
73'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	H
74'	$-CH_2-CH(NR_5R_6)-COOR_8$	H	$COCH_3$	CH_3	-	H	H
75'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	CH_3	-	H	H
76'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	H	H	-	H	H
77'	$-CH_2-\underset{\underset{NR_5R_6}{\vert}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	H
78'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	H
79'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	H
80'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	H

Table 2 (continued)

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
81'	$-CH_2-CH_3$	-	-	-	-	H	10-OH
82'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	10-OH
83'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	10-OH
84'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	10-OH
85'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	H	CH_3	-	H	10-OH
86'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	H	H	-	H	10-OH
87'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	10-OH
88'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	10-OH
89'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	10-OH
90'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	10-OH
91'	$-CH_2-CH_3$	-	-	-	-	H	10,11-OCH_2O-
92'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	10,11-OCH_2O-
93'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	10,11-OCH_2O-
94'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	$COCH_3$	CH_3	-	H	10,11-OCH_2O-
95'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	H	CH_3	-	H	10,11-OCH_2O-
96'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	H	H	-	H	10,11-OCH_2O-
97'	$-CH_2-\underset{\underset{NR_5R_6}{|}}{CH}-COOR_8$	H	$COCH_3$	H	-	H	10,11-OCH_2O-
98'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	10,11-OCH_2O-
99'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	10,11-OCH_2O-
100'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	10,11-OCH_2O-

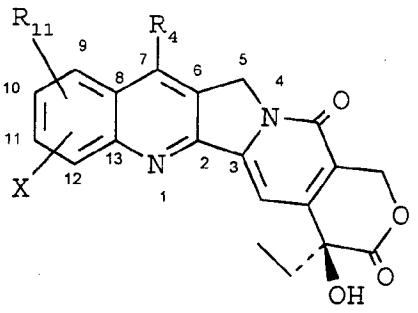
Table 2 (continued)

Compound	9-substituent	R_5	R_6	R_8	R_9	R_4	X
101'	$-CH_2-CH_3$	-	-	-	-	H	10-OCH_3
102'	$-(CH_2)_2-COOR_8$	-	-	CH_3	-	H	10-OCH_3
103'	$-(CH_2)_2-COOR_8$	-	-	H	-	H	10-OCH_3
104'	$-CH_2-\underset{\displaystyle NR_5R_6}{\underset{\vert}{CH}}-COOR_8$	H	$COCH_3$	CH_3	-	H	10-OCH_3
105'	$-CH_2-\underset{\displaystyle NR_5R_6}{\underset{\vert}{CH}}-COOR_8$	H	H	CH_3	-	H	10-OCH_3
106'	$-CH_2-\underset{\displaystyle NR_5R_6}{\underset{\vert}{CH}}-COOR_8$	H	H	H	-	H	10-OCH_3
107'	$-CH_2-\underset{\displaystyle NR_5R_6}{\underset{\vert}{CH}}-COOR_8$	H	$COCH_3$	H	-	H	10-OCH_3
108'	$-(CH_2)_2-COR_9$	-	-	-	CH_3	H	10-OCH_3
109'	$-(CH_2)_2-COR_9$	-	-	-	Ph	H	10-OCH_3
110'	$-(CH_2)_2-COR_9$	-	-	-	NH_2	H	10-OCH_3

In Tables 1 and 2, the symbols Et and Ph stand respectively for ethyl and phenyl.

The present invention includes also in its scope a process for preparing the compounds of formula (I) as defined above, said process comprising

1) reacting a compound of formula (II)



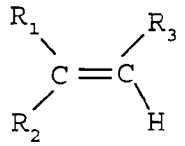
(II)

wherein

R_{11} is a halogen atom, $-OSO_2R_{12}$ wherein R_{12} is C_1-C_5 alkyl unsubstituted or substituted at the terminal carbon atom by one, two or three halogen atoms or an optionally substituted phenyl ring;

R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; and

X is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkanoyloxy, benzoyloxy, amino hydroxy, nitro, halogen or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, with a compound of formula (III)



(III)

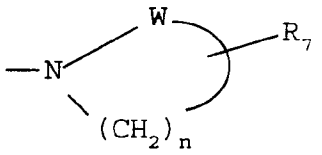
wherein

R_1, R_2 and R_3 are as defined under (a) or (b) below:

(a) R_1 and R_2 are each independently hydrogen; C_1-C_4 alkyl; C_3-C_7 cycloalkyl; phenyl C_1-C_6 alkyl; an optionally substituted phenyl ring;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen, C_1-C_6 alkyl or benzyl and the other is hydrogen, C_1-C_6 alkanoyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted phenoxycarbonyl or phenyl C_1-C_6 alkoxycarbonyl, or R_5 and R_6, combined together with the

nitrogen atom to which they are linked, form a 4-7 membered saturated, optionally substituted, heteromonocyclic ring, represented by a group (G)



(G)

wherein W is -C=O, R_7 is hydrogen or C_1-C_6 alkyl and n is an integer of 2 to 5;

$COOR_8$ wherein R_8 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_6 alkyl, an optionally substituted phenyl ring, $NR_{10}R_{11}$ wherein R_{10} and R_{11} are each independently hydrogen or C_1-C_6 alkyl; and

R_3 is hydrogen, C_1-C_6 alkyl or an optionally substituted phenyl; or

(b) R_1 and R_3, combined together, form a 5-8 membered, optionally substituted carbomonocyclic ring; and

R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_7 cycloalkyl;

so obtaining a compound of formula (I) wherein the symbol ---- represents a double bond;

and, if desired,

2) reducing a compound of formula (I) as obtained under step 1) into a corresponding compound of formula (I) wherein the symbol ---- represents a single bond, and/or if desired, salifying a compound of formula (I).

The starting compounds of formula (II) have a 20 (S)-configuration which is retained through the process leading to the compounds of formula (I). The compounds of formula (II) are typically free of the corresponding 20 (R)-isomers. However, said process may be applied to a racemic mixture of a compound of formula (II) and the corresponding 20 (R)-isomer.

In that case, a racemic mixture of a compound of formula (I) and a 20 (R)- isomer of a compound of formula (I) is obtained. When one or more new stereogenic centers are created in one of the above mentioned steps, all the possible isomers, diastereoisomers, epimers, and geometric isomers, are included in the present disclosure.

The reaction reported under step 1) may be performed in a suitable solvent, in the presence of catalytic amounts, i.e. from 0.0001 to 0.2 molar equivalents, of a compound of formula

$$ML_q\ L'_r$$

wherein

M represents Palladium, Nickel or Platinum.

L and L', which may be the same or different represent an anion such as, e.g. a halide or an acetate or a neutral molecule such as, e.g., a solvent molecule, a phosphine, a phosphite or a diamine; and

q and r may vary from 0 to 4,

provided that q + r is at least 1,

at a temperature of from about -20°C to about 200°C, preferably from about 20°C to about 100°C, for a time which may vary from few minutes to several days, such as, e.g., from 5 minutes to 3 days, preferably from about one hour to about one day, optionally in the presence of a suitable organic or inorganic base, and optionally in the presence of lithium halides, such as, e.g., LiCl, or LiBr.

Suitable solvents include, e.g., dimethylformamide (DMF), acetonitrile, dimethylsulphoxide (DMSO), $CHCl_3$, dioxane, tetrahydrofuran (THF) and mixtures thereof.

Suitable inorganic bases include, e.g., salts with alkali or alkaline earth metals, such as, for example, $NaHCO_3$, Na_2CO_3, or NaOAc.

Suitable organic bases may be, for example, trialkyalmines, such as, e.g., triethylamine or diisopropylethylamine; or heteroaromatic bases such as, e.g., pyridine, or 2,6,-C_1-C_6 alkyl substituted pyridines, such as, e.g., 2,6 lutidine.

Preferred groups which L and/or L' may represent are halides; acetates; phosphines such as, e.g., triphenylphosphine or chelating diphosphines, such as, e.g., bis(diphenylphosphino)methane, 1,2- and 1,3-bis (diphenyl phosphino)propane, 1,4-bis(diphenylsphsphino)- butane or 1,1'-bis(diphenylphosphino)ferrocene (DPPF).

The molar ratio of transition metal atom and/or is general from 1:1 to 1:4.

The reduction reported under item 2) may be performed reacting a compound of formula (I) as obtained under item 1) by using suitable reducing agents, in the presence of suitable catalysts.

Suitable catalysts for the abovesaid reduction are metals known to perform multiple bond reduction such as, e.g., Palladium, Platinum oxide, Platinum, Rhodium, Nickel or Ruthenium.

Suitable reducing agents for the abovesaid reduction are molecular hydrogen or hydrogen sources such as, for instance, triethylammonium formate, formic acid, tributyltin hydride, cyclohexadiene, etc., in a suitable solvent such as, e.g., dimethylformamide (DMF), CH_3OH, acetic acid, $CHCl_3$, dioxane, or mixtures thereof, at a temperature of from about 0°C to about 100°C, for a time of from 1 hour to 3 days, at a pressure of from about 1 atm to about 100 atm.

The starting materials used in this disclosure are known compounds or may be obtained following known methods. For instance, 9-halogeno camptothecin, 10-halogeno camptothecin, 11-halogeno camptothecin, and 12-halogeno camptothecin may be

prepared according, to Sawada, S., et al., Chem. Pharm. Bull. 39, 3183-3188 (1991).

For instance, 10-hydroxy-9-halogeno camptothecin, 10-methoxy-9-halogeno camptothecin, and 10,11-methylendioxy-9-halogeno camptothecin may be prepared starting from the corresponding 10 or 10,11 substituted 9-amino-derivatives, prepared by known procedures (see, for instance, Wall et al. J.Med.Chem. 1993, 36,2689-2700, or Wani et al. J. Med. Chem. 1986, 29, 2358-2363), and then following the above cited reference.

For instance, 9-trifluoromethansulfonyloxy camptothecin,
10-trifluoromethansulfonyloxy camptothecin,
11-tri fluoro methansulfonyloxy camptothecin,
12-trifluoromethansulfonyloxy camptothecin,
10-hydroxy-9-trifluoromethansulfonyloxy camptothecin,
10-methoxy-9-trifluoromethansulfonyloxy camptothecin,
10,11-methylen-dioxy-9-trifluoromethansulfonyloxy camptothecin, 10-p-toluensulfonyloxy camptothecin,
11-p-toluensulfonyloxy camptothecin,
12-p-toluensulfonyloxy camptothecin,
10-hydroxy-9-p-toluensulfonyloxy camptothecin,
10-methoxy-9-p-toluensulfonyloxy camptothecin and
10,11-methylen-dioxy-9-p-toluensulfonyloxy camptothecin were prepared from the corresponding hydroxy derivatives obtained, in turn, as described in the references cited above, and treatment with suitable sulfonylating agents.

The compounds of the present invention are endowed with antitumor activity, for example against leukaemia and solid tumors such as, for example, colon and rectal tumors.

The antitumor activity of the compounds of the present invention is shown, for example, by the fact that they have been found to possess antileukaemic activity when tested

according to the method described in: J.Med.Chem. 1993, 36, 2689, using the L1210 murine lymphoid leukemia model.

As an example, the activity of (E)-9-(2-methoxycarbonyl-ethenyl) camptothecin (internal code FCE 28681) and 9-(2-methoxycarbonyl-ethyl) camptothecin (internal code FCE 29559) were tested according to the following method (a).

The compounds were dissolved in dimethylsulfoxide (DMSO) at a final concentration of 0.5%. The percentage of DMSO solution does not affect the cellular growth.

Method (a): evaluation of cytotoxic activity

L1210 murine leukemia cells were grown in vitro as a floated cells in RPMI 1640 medium supplemented with 10% fetal calf serum, 1% L-glutamine 200 mM, 1% of B-mercaptoethanol 1 mM, 100 UI/ml penicillin and 100 µg streptomycin. For assaying the cytotoxic activity, exponentially growing cells were seeded at the concentration of $5x10^4$ cells/ml and exposed to graded doses of the compounds under evaluation for 48h at 37°C in an humidified atmosphere of 5% CO_2. The number of surviving cells was determined with a Coulter Counter; results are expressed as IC50 (dose causing 50% inhibition of cell growth in treated cultures relative to untreated controls after 48h treatment) in this assay, (E)-9-(2-methoxycarbonyl-ethenyl) camptothecin (internal code FCE 28681) and 9-(2-methoxycarbonyl-ethyl) camptothecin (internal code FCE 29559) were tested and the obtained results are reported on Table 1 below.

Table 1

COMPOUND	IC_{50} (ng/ml)
FCE 28681	3.3 ± 1.8
FCE 29559	2.7 ± 0.5

A human or animal body may thus be treated by a method which comprises the administration thereto of a pharmaceutically effective amount of a compound of formula (I) or salt thereof. The condition of the human or animal can thereby be improved.

Pharmaceutical compositions containing the novel camptothecin analogues according to the invention are also within the scope of the present invention.

These pharmaceutical compositions may contain any quantity of a camptothecin analog which is effective to exhibit any antitumor activity in vivo. Mammalian such as humans are treatable with the inventive compositions. Typical in vivo doses within the scope of the invention are from 0.1-60 mg of camptothecin analog per kg of body weight. A particularly preferred range is 1-40 mg/kg.

There may also be included as part of the composition pharmaceutically compatible binding agents, and/or adjuvant materials. The active materials can also be mixed with other active materials which do not impair the desired action and/or supplement the desired action. The active materials according to the present invention can be administered by any route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred mode of administration of the compounds of the invention is oral.

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the aforesaid compounds may be incorporated with excipients and used in the form of tablets, capsules, elixirs, syrups and the like. These preparations should contain at least 0,1% of active compound but may be varied depending upon the particular form.

The tablets, pills, capsules, troches and the like may contain the following ingredients: a binder such as microcrystalline cellulose, gumtragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, corn starch and the like; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin or flavouring agent such as peppermint, methyl salicylate, or orange flavouring may be added. When the dosage unit form is a capsule, it may contain, in addition to material of the above type, a liquid carrier such as fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar shellac, or other enteric coating agents.

A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colouring and flavours.

Material used in preparing these various compositions should be pharmaceutically pure and non toxic in the amount used.

For the purpose of parenteral therapeutic administration, the active ingredient may be incorporated into a solution or suspension.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The

parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The dosage values will vary with the specific severity of the disease condition to be alleviated. Good results are achieved when the compounds described herein are administered to a subject requiring such treatment as an effective oral, parenteral or intravenous dose. It is to be understood that for any particular subject, specific dosage regimens should be adjusted to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and they do not limit the scope or practice of the invention. The dosages may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

The following examples illustrates but do not limit the invention.

The number into bracket reported before the chemical name of the compounds prepared according to the following examples corresponds to the number given to the preferred compounds listed on pages 6-18 of the present specification.

Preparation of the starting materials

Method A:

9-bromo camptothecin

2.15 g of $NaNO_2$ in 40 mL of H_2O were dropped at 5°C into a solution of 9 g of 9-amino-camptothecin in 850 mL of 16% HBr. After 1 hr at r.t. the solution was dropped in a flask containing 19 g of CuBr in 200 mL of 16% HBr at 70°C. The reaction was allowed to stay at 70°C for 2 hr, then it was

poured in cold water. The precipitate was filtered and the mother liquors were extracted with CH_2Cl_2; the organic extract dried and evaporated was combined with the precipitate and purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 95/5) to give 8.19 g of the title product. (HPLC assay : 97.3%)

^{1}H-NMR 400 MHz (DMSO-d6): d = 8.87 (s, 1H), 8.20 (d, J = 8.5, 1H), 8.06 (d, J = 7.32, 1H), 7.81-7.75 (m, 1H), 7.35 (s, 1H), 6.53 (s, 1H), 5.42 (s, 2H), 5.32 (s, 2H), 1.89-1.82 (m, 2H), 0.87 (t, J = 7.32, 3H).

MS (FD) : $M^{+\cdot}$ = 427.

By analogy starting from the corresponding amino derivatives, the following bromo derivatives were prepared:

10-bromo camptothecin;

11-bromo camptothecin;

12-bromo camptothecin;

10-hydroxy-9-bromo camptothecin;

10-methoxy-9-bromo camptothecin; and

10,11-methylendioxy-9-bromo camptothecin.

Method B:

10-trifluoromethansulfonyloxy camptothecin

1.25 g of 10-hydroxy camptothecin were dissolved in 35 mL of DMF and 2 mL of Et_3N and 1.5 g of N,N-Bis-(trifluormethan-sulfonyl)-anilin were added. The solution was heated at 50°C for 1 hr, then poured in water; the precipitate was filtered and the mother liquors were extracted with CH_2Cl_2. The organic extract, dried (Na_2SO_4) and evaporated, was combined with the precipitate and purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 98/2). 1 g of the title product was obtained. (HPLC assay: 97%)

^{1}H-NMR 400 MHz (DMSO-d6): d = 8.81 (s, 1H), 8.43-8.32 (m, 2 H), 7.99-7.94 (m, 1H), 7.36 (s, 1H), 6.54 (s, 1H), 5.42 (s, 2H), 5.32 (s, 2H), 1.90-1.81 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H).

MS (FD): $M^{+\cdot}$ = 496

By analogy, starting from the corresponding nitro and amino derivatives, the following sulfonyl derivatives were prepared:

9-trifluoromethansulfonyloxy camptothecin;

11-trifluoromethansulfonyloxy camptothecin;

12-trifluoromethansulfonyloxy camptothecin;

10,11-methylendioxy-9-trifluoromethansulfonyloxy camptothecin;

10-p-toluensulfonyloxy camptothecin;

11-p-toluensulfonyloxy camptothecin;

12-p-toluensulfonyloxy camptothecin;

10-methoxy-9-p-toluensulfonyloxy camptothecin; and

10,11-methylendioxy-9-p-toluensulfonyloxy camptothecin.

Example 1

12-vinyl camptothecin (65)

1 g of 12-Br-camptothecin was dissolved in 20 mL of DMF; in an Ar atmosphere, 0.72 mL of Et_3N, 3.61 mL of vinyltrimethylsilane, 0.071 g of DPPF and 0.026 g of $Pd(OAc)_2$ were added sequentially. The reaction mixture was heated at 100°C for 1 hr and then treated with CH_2Cl_2 and water. The aqueous phase was extracted twice with CH_2Cl_2 and the organic extracts were collected, dried (Na_2SO_4), and evaporated. The residue was dissolved in 20 mL of CH_2Cl_2, 10 mL of CF_3COOH were added and the solution was left at r.t. for 24 hr. The reaction was worked up as before and the product was purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 95/5) to give 0.59 g of the title product. (HPLC assay : 97%).

^{1}H-NMR 400 MHz (DMSO-d6): d = 8.67 (s, 1H), 8.14-8.00 (m, 3H), 7.69 (t, J=7.9Hz, 1H), 7.36 (s, 1H), 6.54 (s, 1H), 6.14 (dd, J=1.2, 17.9Hz, 1H), 5.57 (d, J=12.3Hz, 1H), 5.42 (s, 2H), 5.28 (s, 2H), 1.94-1.80 (m, 2H), 0.88 (t, J=7.0Hz, 3H).
MS (FD): $M^{+\cdot}$ = 374.

By analogy the following compounds were obtained (Table 1):
9-vinyl camptothecin (1);
7-ethyl-9-vinyl camptothecin (9);
10-vinyl camptothecin (17);
7-ethyl-10-vinyl camptothecin (25);
10-hydroxy-9-vinyl camptothecin (33);
10,11-methylendioxy-9-vinyl camptothecin (41);
10-methoxy-9-vinyl camptothecin (49);
11-vinyl camptothecin (57);
9-amino-10-vinyl camptothecin (73); and
7-ethyl-9-amino-10-vinyl camptothecin (81).

Example 2

(Z)-12-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (68)

2 g of 12-Br-camptothecin were dissolved in 40 mL of DMF; in an Ar atmosphere, 0.72 mL of Et_3N, 3.32 g of Methyl 2-acetamidoacrylate, 0.14 g of DPPF and 0.052 g of $Pd(OAc)_2$ were added sequentially. The reaction mixture was heated at 100°C for 24 hr. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with water. The organic extract was dried (Na_2SO_4) and the solvent removed under vacuo. The crude was purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 98/2) to give 1.72 g of the title product. (HPLC assay : 97.4%)

^{1}H-NMR 400 MHz (DMSO-d6): d = 9.79 (s, 1H), 8.73 (s, 1H), 8.32 (s, 1H), 8.18 (d, J = 7.03 Hz, 1H), 8.15 (d, J = 7.91 Hz, 1H), 7.75 (t, J = 7.62 Hz, 1H), 7.34 (s, 1H), 6.56 (s, 1H), 5.43 (s, 2H), 5.43 (s, 2H), 3.78 (s, 3H), 1.98 (s, 3H), 1.88 (m, 2H), 0.88 (t, J = 7.3Hz, 3H).

MS (FD) : $M^{+\cdot}$ = 489.

When a solution of (Z)-12-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin is allowed to stand at room temperature for 2 weeks, a 50/50 mixture of E and Z isomers is obtained.

By analogy the following compounds were obtained (Table 1):

10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (20);

10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (21);

7-ethyl-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (28);

7-ethyl-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (29);

10-hydroxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (36);

10-hydroxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (37);

10,11-methylendioxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (44);

10,11-methylendioxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (45);

10-methoxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (52);

10-methoxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (53);

11-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (60);

11-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (61);

12-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (69);

9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (76);

9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (77);

7-ethyl-9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (84); and

7-ethyl-9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (85).

Example 3

(E)-12-(2-methoxycarbonyl-ethenyl) camptothecin (66)

5 g of 12-Br-camptothecin were dissolved in 50 mL of DMF; in an Ar atmosphere, 1.5 mL of Et_3N, 4.6 mL of Methyl acrylate, 0.28 g of DPPF and 0.11 g of $Pd(OAc)_2$ were added sequentially. The reaction was heated at 100°C for 18 hr then worked up diluting with CH_2Cl_2 and washing twice with water. The organic phase was dried (Na_2SO_4) evaporated and the residue was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 98/2) to give 4.1 g of the title product. (HPLC assay : 92.34%)

^{1}H-NMR 400 MHz (DMSO-d6) : d = 8.94 (d, J = 16.2 Hz, 1H), 8.73 (s, 1H), 8.39 (d, J = 6.7 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.75 (t, J = 7.6, 1H), 7.36 (s, 1H), 7.00 (d, J = 16.2 Hz, 1H), 6.59 (s, 1H), 5.43 (s, 2H), 5.30 (s, 2H), 3.80 (s, 3H), 1.88 (m, 2H), 0.89 (t, 3H).

MS (FD) : $M^{+\cdot}$ = 432.

By analogy the following compounds were obtained (Table 1):

11-(2-methoxycarbonyl-ethenyl) camptothecin (58);

11-(2-hydroxycarbonyl-ethenyl) camptothecin (59);

11-(3-oxo-but-1-enyl) camptothecin (62);

11-(3-oxo-3-phenyl-propenyl) camptothecin (63);

11-(2-aminocarbonyl-ethenyl) camptothecin (64);

12-(2-hydroxycarbonyl-ethenyl) camptothecin (67);

12-(3-oxo-but-1-enyl) camptothecin (70);

12-(3-oxo-3-phenyl-propenyl) camptothecin (71);

12-(2-aminocarbonyl-ethenyl) camptothecin (72);

9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (74);

9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (75);

9-amino-10-(3-oxo-but-1-enyl) camptothecin (78);

9-amino-10-(3-oxo-3-phenyl-propenyl) camptothecin (79);

9-amino-10-(2-aminocarbonyl-ethenyl) camptothecin (80);

7-ethyl-9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (82);

7-ethyl-9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (83);

7-ethyl-9-amino-10-(3-oxo-but-1-enyl) camptothecin (86);

7-ethyl-9-amino-10-(3-oxo-3-phenyl-propenyl) camptothecin (87); and

7-ethyl-9-amino-10-(2-aminocarbonyl-ethenyl) camptothecin (88).

Example 4

12-(2-methoxycarbonyl-ethyl) camptothecin (52')

1 g of 12-(2-methoxycarbonyl-ethenyl) camptothecin was dissolved in 20 mL of DMF and hydrogenated in presence of 0.1 g of Pd/C at r.t. under 1 atm of H_2. The reaction mixture was filtered through a celite pad washing the celite thoroughly with DMF, the solvent was evaporated and the residue was

purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 98/2) to give 0.82 g of the title product.

^{1}H-NMR 400 MHz (DMSO-d6) : d = 8.60 (s, 1H), 7.92 (dd, J = 1.5, 8.2 Hz, 1H), 7.66 (dd, J = 1.5, 7 Hz, 1H), 7.54 (dd, J = 7, 8.2 Hz, 1H), 7.31 (s, 1H), 6.54 (s, 1H), 5.41 (s, 2H), 5.20 (m, 2H), 3.57 (s, 3H), 3.52-3.49 (m, 2H), 2.84-2.81 (m, 2H), 1.88-1.84 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). MS (FD) : M^+ = 434.

By analogy the following compounds were obtained (Table 2):

11-ethyl camptothecin (41');

11-(2-methoxycarbonyl-ethyl) camptothecin (42');

11-(2-hydroxycarbonyl-ethyl) camptothecin (43');

11-(3-oxo-butyl) camptothecin (48');

11-(3-oxo-3-phenyl-propyl) camptothecin (49');

11-(2-aminocarbonyl-ethyl) camptothecin (50');

9-amino-12-ethyl camptothecin (51');

9-amino-12-(2-methoxycarbonyl-ethyl) camptothecin (52');

9-amino-12-(2-hydroxycarbonyl-ethyl) camptothecin (53');

9-amino-12-(3-oxo-butyl) camptothecin (58');

9-amino-12-(3-oxo-3-phenyl-propyl) camptothecin (59');

9-amino-12-(2-aminocarbonyl-ethyl) camptothecin (60');

10-amino-9-ethyl camptothecin (61');

10-amino-9-(2-methoxycarbonyl-ethyl) camptothecin (62');

10-amino-9-(2-hydroxycarbonyl-ethyl) camptothecin (63');

10-amino-9-(3-oxo-butyl) camptothecin (68');

10-amino-9-(3-oxo-3-phenyl-3-one-propyl) camptothecin (69');

10-amino-9-(2-aminocarbonyl-ethyl) camptothecin (70');

12-ethyl camptothecin (71');

12-(2-hydroxycarbonyl-ethyl) camptothecin (73');

12-(3-oxo-butyl) camptothecin (78');

12-(3-oxo-3-phenyl-propyl) camptothecin (79');

12-(2-aminocarbonyl-ethyl) camptothecin (80');

10-hydroxy-9-ethyl camptothecin (81');

10-hydroxy-9-(2-methoxycarbonyl-ethyl) camptothecin (82');

10-hydroxy-9-(2-hydroxycarbonyl-ethyl) camptothecin (83');

10-hydroxy-9-(3-oxo-butyl) camptothecin (88');

10-hydroxy-9-(3-oxo-3-phenyl-3-one-propyl) camptothecin (89');

10-hydroxy-9-(2-aminocarbonyl-ethyl) camptothecin (90');

10-methoxy-9-ethyl camptothecin (101');

10-methoxy-9-(2-methoxycarbonyl-ethyl)camptothecin (102');

10-methoxy-9-(2-hydroxycarbonyl-ethyl) camptothecin (103');

10-methoxy-9-(3-oxo-butyl) camptothecin (108');

10-methoxy-9-(3-oxo-3-phenyl-propyl) camptothecin (109'); and

10-methoxy-9-(2-aminocarbonyl-ethyl) camptothecin (110').

Example 5

12-[(2R,S)(2-acetylamino-2-methoxycarbonyl)-ethyl] camptothecin (74')

1 g of (Z)-12-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin was dissolved in DMF. After addition of 0.15 g of Pd/C, the product was hydrogenated at r.t. for 28 hr. The reaction mixture was filtered through a pad of celite and evaporated; the residue was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH) to give 0.89 g of the title product. (HPLC assay : 96.7%)

^{1}H-NMR 400 MHz (DMSO-d6) : d = 8.66 (s, 1H), 8.49-8.43 (m, 1H), 7.99 (d, J = 7.33 Hz, 1H), 7.63-7.60 (m, 2H), 7.42 (s, 1/2H), 7.40 (s, 1/2H), 6.56 (s, 1/2H), 6.54 (s, 1/2H), 5.42 (s, 2H), 5.30 (s, 2H), 4.75-4.66 (m, 1H), 3.96-3.88 (m, 1H), 3.55 (s, 1.5H), 3.49 (s, 1.5H), 3.36-3.31 (m, 1H), 1.81-1.87 (m, 2H), 1.77 (s, 1.5H), 1.75 (s, 1.5H), 0.92-0.94 (m, 3H).

MS (FD) : $M^{+\cdot}$ = 491

By analogy the following compounds may be obtained (Table 2):

9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (4');
9-[(2-amino-2-methoxycarbonyl]-ethyl) camptothecin (5');
9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (6');
9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (7');
7-ethyl-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (14');
7-ethyl-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (15');
7-ethyl-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (16');
7-ethyl-9-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (17');
10-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (24');
10-[(2-amino-2-methoxycarbonyl]-ethyl) camptothecin (25');
10-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (26');
10-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (27');
7-ethyl-10-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (34');
7-ethyl-10-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (35');
7-ethyl-10-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (36');
7-ethyl-10-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (37');
11-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (44');
11-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (45');
11-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (46');
11-[(2-acetylamino-2-hydroxycarbonyl)-ethyl]camptothecin (47');

9-amino-12-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (54');
9-amino-12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (55');
9-amino-12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (56');
9-amino-12-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (57');
10-amino-9-[(2-acetylamino-2-methoxycarbonyl)-ethyl] camptothecin (64');
10-amino-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (65');
10-amino-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (66');
10-amino-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (67');
12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (75');
12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (76');
12-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (77');
10-hydroxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (84');
10-hydroxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (85');
10-hydroxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (86');
10-hydroxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (87');
10,11-methylendioxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)-camptothecin (94');
10,11-methylendioxy-9-[(2-amino-2-methoxycarbonyl]-ethyl) camptothecin (95');

10,11-methylendioxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (96');

10,11-methylendioxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl]-camptothecin (97');

10-methoxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (104');

10-methoxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (105');

10-methoxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (106'); and

10-methoxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (107').

Example 7

(Z)-9-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (4)

5 g of 9-Br-camptothecin were dissolved in 50 mL of DMF; in an Ar atmosphere, 1.8 mL of Et_3N, 8.3 g of Methyl 2-acetamidoacrylate, 0.35 g of DPPF and 0.13 g of $Pd(OAc)_2$ were added sequentially. The reaction mixture was heated at 100°C for 7 hr and then taken up with CH_2Cl_2 and water. The organic extract was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 98/2) to give 4.89 g of the title product. (HPLC assay : 98.7%)

^{1}H-NMR 400 MHz (DMSO-d6) : d = 9.63 (s, 1H), 8.73 (s, 1H), 8.16 (d, J = 8.54 Hz, 1H), 7.89-7.85 (m, 1H), 7.77 (d, J = 7.26, 1H), 7.62 (s, 1H), 7.34 (s, 1H), 6.52 (s, 1H), 5.41 (s, 2H), 5.25 (s, 2H), 3.76 (s, 3H), 1.87-1.83 (m, 5H), 0.86 (t, J = 7.26, 3H).

MS (FD) : M^+ = 489

When a solution of (Z)-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin is allowed to stand at r.t. for 2 weeks, a 50/50 mixture of E and Z isomers is obtained. The ^{1}H-NMR spectrum of (E)-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin is:

d = 10.32 (s, 1H), 8.74 (s, 1H), 8.09 (d, J = 8.79, 1H), 7.80-7.76 (m, 1H), 7.63 (s, 1H), 7.37-7.34 (m, 2H), 6.53 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H), 3.42 (s, 3H), 2.02 (s, 3H), 1.89-1.82 (m, 2H), 0.87 (t, J = 7.26, 3H).

By analogy the following compounds were prepared (Table 1):
9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (5);
7-ethyl-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (12); and
7-ethyl-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (13).

Example 8

(E)-9-(2-methoxycarbonyl-ethenyl) camptothecin (2)

1 g of 9-Br-camptothecin was dissolved in 11 mL of DMF; 0.3 mL of Et_3N, 0.92 mL of Methyl acrylate, 0.056 g of DPPF, 0.022 g of $Pd(OAc)_2$ were added sequentially under an Ar atmosphere. The reaction mixture was heated at 100°C; after 3 hr the reaction is over and a white yellowish precipitate is present. The precipitate is filtered and washed twice with DMF and twice with Et_2O. The product is crystallized ($CHCl_3$/DMF) to give 0.58 g of the title product. (HPLC assay : 95.59%)

^{1}H-NMR 400 MHz (DMSO-d6) : d = 9.07 (s, 1H), 8.45 (d, J = 15.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 7.1, 1H), 7.88 (dd, J = 7.6 Hz, J' = 8.2 Hz, 1H), 7.34 (s, 1H), 6.80 (d, J =

15.8 Hz, 1H), 6.53 (s, 1H), 5.42 (s, 2H), 5.27 (s, 2H), 3.79 (s, 3H), 1.86 (m, 2H), 0.87 (t, 3H).

MS (FD) : $M^{+\cdot}$ = 432.

By analogy the following compounds were prepared (Table 1):

9-(2-hydroxycarbonyl-ethenyl) camptothecin (3);

9-(2-aminocarbonyl-ethenyl) camptothecin (8);

9-(3-oxo-but-1-enyl) camptothecin (6);

9-(3-oxo-3-phenyl-propenyl) camptothecin (7);

7-ethyl-9-(2-methoxycarbonyl-ethenyl) camptothecin (10);

7-ethyl-9-(2-hydroxycarbonyl-ethenyl) camptothecin (11);

7-ethyl-9-(3-oxo-but-1-enyl) camptothecin (14);

7-ethyl-9-(3-oxo-3-phenyl-propenyl) camptothecin (15);

7-ethyl-9-(2-aminocarbonyl-ethenyl) camptothecin (16);

10,11-methylendioxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (42);

d10,11-methylendioxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (43);

10,11-methylendioxy-9-(3-oxo-but-1-enyl) camptothecin (46);

10,11-methylendioxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (47);

10,11-methylendioxy-9-(2-aminocarbonyl-ethenyl)camptothecin (48);

10-methoxy-9-(2-methoxycarbonyl-ethenyl)camptothecin 50);

10-methoxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (51);

10-methoxy-9-(3-oxo-but-1-enyl) camptothecin (54);

10-methoxy-9-(3-oxo-3-phenyl-propenyl) camptothecin (55); and

10-methoxy-9-(2-aminocarbonyl-ethenyl) camptothecin (56).

Example 9

9-(2-methoxycarbonyl-ethyl) camptothecin (2')

1.4 g of (E)-9-(2-methoxycarbonyl-ethenyl) camptothecin are dissolved in 400 mL of DMF, 0.3 g of Pd/C are added and the mixture is hydrogenated at r.t. (1 atm H_2) for 3 hr. The reaction mixture is filtered and the solvent is evaporated. The residue is purified by flash chromatography (eluent : CH_2Cl_2/CH_3OH = 98/2) to give 1.2 g of the title product.

^{1}H-NMR 400 MHz (DMSO-d6) : d = 8.89 (s, 1H), 8.03 (d, J = 8.49 Hz, 1H), 7.79-7.73 (m, 1H), 7.55 (d, J = 7.03, 1H), 7.33 (s, 1H), 6.51 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H), 3.59 (s, 3H), 3.42-3.36 (m, 2H), 2.88-2.77 (m, 2H), 1.91-1.80 (m, 2H), 0.87 (t, J = 7.33, 3H).

MS (FD) : $M^{+\cdot}$ = 434.

By analogy the following compounds were prepared (Table 2):

9-ethyl camptothecin (1');

9-(2-hydroxycarbonyl-ethyl) camptothecin (3');

9-(3-oxo-butyl) camptothecin (8');

9-(3-oxo-3-phenyl--propyl) camptothecin (9');

9-(2-aminocarbonyl-ethyl) camptothecin (10');

7-ethyl-9-ethyl camptothecin (11');

7-ethyl-9-(2-methoxycarbonyl-ethyl) camptothecin (12');

7-ethyl-9-(2-hydroxycarbonyl-ethyl) camptothecin (13');

7-ethyl-9-(3-oxo-butyl) camptothecin (18');

7-ethyl-9-(3-oxo-3-phenyl-propyl) camptothecin (19');

7-ethyl-9-(2-aminocarbonyl-ethyl) camptothecin (20');

10-ethyl camptothecin (21');

10-(2-methoxycarbonyl-ethyl) camptothecin (22');

10-(2-hydroxycarbonyl-ethyl) camptothecin (23');

10-(3-oxo-butyl) camptothecin (28');

10-(3-oxo-3-phenyl-propyl) camptothecin (29');

10-(2-aminocarbonyl-ethyl) camptothecin (30');

7-ethyl-10-ethyl camptothecin (31');

7-ethyl-10-(2-methoxycarbonyl-ethyl) camptothecin (32');
7-ethyl-10-(2-hydroxycarbonyl-ethyl) camptothecin (33');
7-ethyl-10-(3-oxo-butyl) camptothecin (38');
7-ethyl-10-(3-oxo-3-phenyl-propyl) camptothecin (39');
7-ethyl-10-(2-aminocarbonyl-ethyl) camptothecin (40');
10,11-methylendioxy-9-ethyl camptothecin (91');
10,11-methylendioxy-9-(2-methoxycarbonyl-ethyl)camptothecin (92');
10,11-methylendioxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (93');
10,11-methylendioxy-9-(3-oxo-butyl) camptothecin (98');
10,11-methylendioxy-9-(3-oxo-3-phenyl-propyl)camptothecin (99'); and
10,11-methylendioxy-9-(2-aminocarbonyl-ethyl)camptothecin (100').

Example 10

(E)-10-(2-methoxycarbonyl-ethenyl) camptothecin (18)

1 g of 10-trifluoromethansulfonyloxy camptothecin was dissolved in 10 mL of DMF; in an Ar atmosphere, 0.31 mL of Et_3N, 0.91 mL of Methyl acrylate, 0.062 g of DPPF and 0.023 g of $Pd(OAc)_2$ were added sequentially. The reaction was heated at 80°C for 24 hr then worked up diluting with CH_2Cl_2 and washing twice with brine. The organic phase was dried (Na_2SO_4) evaporated and the residue was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 99/1) to give 0.5 g of the title product. (HPLC assay : 97%)

^{1}H-NMR 400 MHz (DMSO-d6) : d = 8.65 (s, 1H), 8.42 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 16.1 Hz, 1H), 7.34 (s, 1H), 6.87 (d, J = 16.1 Hz, 1H), 6.53 (s, 1H), 5.41 (s, 2H), 5.28 (s, 2H), 3.76 (s, 3H), 1.88-1.82 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H).

MS (FD) : $M^{+\cdot}$ = 432.

By analogy the following compounds were prepared (Table 1):

10-(2-hydroxycarbonyl-ethenyl) camptothecin (19);

10-(3-oxo-but-1-enyl) camptothecin (22);

10-(3-oxo-3-phenyl-propenyl) camptothecin (23);

10-(2-aminocarbonyl-ethenyl) camptothecin (24);

7-ethyl-10-(2-methoxycarbonyl-ethenyl) camptothecin (26);

7-ethyl-10-(2-hydroxycarbonyl-ethenyl) camptothecin (27);

7-ethyl-10-(3-oxo-but-1-enyl) camptothecin (30);

7-ethyl-10-(3-oxo-3-phenyl-propenyl) camptothecin (31);

7-ethyl-10-(2-aminocarbonyl-ethenyl) camptothecin (32);

10-hydroxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (34);

10-hydroxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (35);

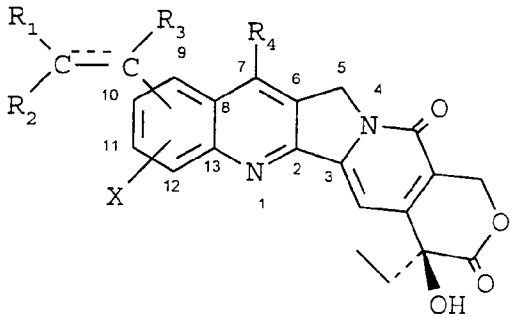
10-hydroxy-9-(3-oxo-but-1-enyl) camptothecin (38);

10-hydroxy-9-(3-oxo-3-phenyl-propenyl) camptothecin (39); and

10-hydroxy-9-(2-aminocarbonyl-ethenyl) camptothecin (40).

CLAIMS

1. Substituted camptothecin derivatives of formula (I)



(I)

wherein

the symbol ---- represents a single or double bond;

R_1, R_2 and R_3 are as defined under (a) or (b) below:

(a) R_1 and R_2 are, each independently,

hydrogen;

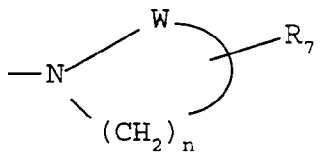
C_1-C_4 alkyl;

C_3-C_7 cycloalkyl;

phenyl C_1-C_6 alkyl;

an optionally substituted phenyl ring;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen, C_1-C_6 alkyl or benzyl and the other is hydrogen, C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, an optionally substituted phenoxycarbonyl or phenyl C_1-C_6 alkoxycarbonyl, or R_5 and R_6, combined together with the nitrogen atom to which they are linked, form a 4-7 membered saturated, optionally substituted, heteromonocyclic ring residue, represented by a group (G)



(G)

wherein W is -C=O, R_7 is hydrogen or C_1-C_6 alkyl and n is an integer of 2 to 5;

$COOR_8$ wherein R_8 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_6 alkyl, an optionally substituted phenyl ring or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are, each independently, hydrogen or C_1-C_6 alkyl; and

R_3 is hydrogen, C_1-C_6 alkyl or an optionally substituted phenyl ring; or

(b) R_1 and R_3, combined together, form a 5-8 membered, optionally substituted, carbomonocyclic ring; and

R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_7 cycloalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl;

X is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkanoyloxy, benzoyloxy, amino, hydroxy, nitro, halogen or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to claim 1, wherein the symbol ---- represents a single or a double bond;

R_1 and R_2 are, each independently,

hydrogen;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen and the other is hydrogen C_1-C_6 alkanoyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, phenoxy-carbonyl or phenyl C_1-C_6 alkoxycarbonyl;

$COOR_8$ wherein R_8 is hydrogen or C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, unsubstituted phenyl or $NR_{10}R_{11}$ wherein R_{10} and R_{11} are both hydrogen;

R_3 is hydrogen;

R_4 is hydrogen or C_1-C_6 alkyl;

X is hydrogen, hydroxy, amino, C_1-C_6 alkoxy or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, and the pharmaceutically acceptable salts thereof.

3. A compound selected from:

9-vinyl camptothecin (1);

(E)-9-(2-methoxycarbonyl-ethenyl)camptothecin (2);

9-(2-hydroxycarbonyl-ethenyl)camptothecin (3);

(Z)-9-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (4);

9-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (5);

9-(3-oxo-but-1-enyl)camptothecin (6);

9-(3-oxo-3-phenyl-propenyl)camptothecin (7);

9-(2-aminocarbonyl-ethenyl)camptothecin (8);

7-ethyl-9-vinyl camptothecin (9);

7-ethyl-9-(2-methoxycarbonyl-ethenyl)camptothecin (10);

7-ethyl-9-(2-hydroxycarbonyl-ethenyl)camptothecin (11);

7-ethyl-9-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (12);

7-ethyl-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (13);

7-ethyl-9-(3-oxo-but-1-enyl)camptothecin (14);

7-ethyl-9-(3-oxo-3-phenyl-propenyl)camptothecin (15);

7-ethyl-9-(2-aminocarbonyl-ethenyl)camptothecin (16);

10-vinyl camptothecin (17);

(E)-10-(2-methoxycarbonyl-ethenyl)camptothecin (18);

10-(2-hydroxycarbonyl-ethenyl)camptothecin (19);

10-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (20);

10-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (21);

10-(3-oxo-but-1-enyl)camptothecin (22);

10-(3-oxo-3-phenyl-propenyl)camptothecin (23);

10-(2-aminocarbonyl-ethenyl)camptothecin (24);

7-ethyl-10-vinyl camptothecin (25);

7-ethyl-10-(2-methoxycarbonyl-ethenyl)camptothecin (26);

7-ethyl-10-(2-hydroxycarbonyl-ethenyl)camptothecin (27);

7-ethyl-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (28);

7-ethyl-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (29);

7-ethyl-10-(3-oxo-but-1-enyl)camptothecin (30);

7-ethyl-10-(3-oxo-3-phenyl-propenyl)camptothecin (31);

7-ethyl-10-(2-aminocarbonyl-ethenyl)camptothecin (32);

10-hydroxy-9-vinyl camptothecin (33);

10-hydroxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (34);

10-hydroxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (35);

10-hydroxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (36);

10-hydroxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (37);

10-hydroxy-9-(3-oxo-but-1-enyl)camptothecin (38);

10-hydroxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (39);

10-hydroxy-9-(2-aminocarbonyl-ethenyl)camptothecin (40);

10,11-methylendioxy-9-vinyl camptothecin (41);

10,11-methylendioxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (42);

10,11-methylendioxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (43);

10,11-methylendioxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (44);

10,11-methylendioxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (45);

10,11-methylendioxy-9-(3-oxo-but-1-enyl)camptothecin (46);

10,11-methylendioxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (47);

10,11-methylendioxy-9-(2-aminocarbonyl-ethenyl)camptothecin (48);

10-methoxy-9-vinyl camptothecin (49);

10-methoxy-9-(2-methoxycarbonyl-ethenyl)camptothecin (50);

10-methoxy-9-(2-hydroxycarbonyl-ethenyl)camptothecin (51);

10-methoxy-9-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (52);

10-methoxy-9-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (53);

10-methoxy-9-(3-oxo-but-1-enyl)camptothecin (54);

10-methoxy-9-(3-oxo-3-phenyl-propenyl)camptothecin (55);

10-methoxy-9-(2-aminocarbonyl-ethenyl)camptothecin (56);

11-vinyl camptothecin (57);

11-(2-methoxycarbonyl-ethenyl)camptothecin (58);

11-(2-hydroxycarbonyl-ethenyl)camptothecin (59);

11-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (60);

11-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (61);

11-(3-oxo-but-1-enyl)camptothecin (62);

11-(3-oxo-3-phenyl-propenyl)camptothecin (63);

11-(2-aminocarbonyl-ethenyl)camptothecin (64);

12-vinyl camptothecin (65);

(E)-12-(2-methoxycarbonyl-ethenyl)camptothecin (66);

12-(2-hydroxycarbonyl-ethenyl)camptothecin (67);

(Z)-12-(2-acetylamino-2-methoxycarbonyl-ethenyl)camptothecin (68);

12-(2-acetylamino-2-hydroxycarbonyl-ethenyl)camptothecin (69);

12-(3-oxo-but-1-enyl)camptothecin (70);

12-(3-oxo-3-phenyl-propenyl)camptothecin (71);

12-(2-aminocarbonyl-ethenyl)camptothecin (72);

9-amino-10-vinyl camptothecin (73);

9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (74);

9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (75);

9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (76);

9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (77);

9-amino-10-(3-oxo-but-1-enyl)camptothecin (78);

9-amino-10-(3-oxo-3-phenyl-propenyl)camptothecin (79);

9-amino-10-(2-aminocarbonyl-ethenyl)camptothecin (80);

7-ethyl-9-amino-10-vinyl camptothecin (81);

7-ethyl-9-amino-10-(2-methoxycarbonyl-ethenyl)camptothecin (82);

7-ethyl-9-amino-10-(2-hydroxycarbonyl-ethenyl)camptothecin (83);

7-ethyl-9-amino-10-(2-acetylamino-2-methoxycarbonyl-ethenyl) camptothecin (84);

7-ethyl-9-amino-10-(2-acetylamino-2-hydroxycarbonyl-ethenyl) camptothecin (85);

7-ethyl-9-amino-10-(3-oxo-but-1-enyl)camptothecin (86);

7-ethyl-9-amino-10-(3-oxo-3-phenyl-propenyl)camptothecin (87);

7-ethyl-9-amino-10-(2-aminocarbonyl-ethenyl)camptothecin (88);

9-ethyl camptothecin (1');

9-(2-methoxycarbonyl-ethyl)camptothecin (2');

9-(2-hydroxycarbonyl-ethyl)camptothecin (3');

9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (4');

9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (5');

9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (6');

9-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (7');

9-(3-oxo-butyl)camptothecin (8');

9-(3-oxo-3-phenyl-propyl)camptothecin (9');

9-(2-aminocarbonyl-ethyl)camptothecin (10');

7-ethyl-9-ethyl camptothecin (11');

7-ethyl-9-(2-methoxycarbonyl-ethyl)camptothecin (12');

7-ethyl-9-(2-hydroxycarbonyl-ethyl)camptothecin (13');

7-ethyl-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (14');

7-ethyl-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (15');

7-ethyl-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (16');

7-ethyl-9-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (17');

7-ethyl-9-(3-oxo-butyl)camptothecin (18');

7-ethyl-9-(3-oxo-3-phenyl-propyl)camptothecin (19');

7-ethyl-9-(2-aminocarbonyl-ethyl)camptothecin (20');

10-ethyl camptothecin (21');

10-(2-methoxycarbonyl-ethyl)camptothecin (22');

10-(2-hydroxycarbonyl-ethyl)camptothecin (23');

10-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (24');

10-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (25');

10-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (26');

10-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (27');

10-(3-oxo-butyl)camptothecin (28');

10-(3-oxo-3-phenyl-propyl)camptothecin (29');

10-(2-aminocarbonyl-ethyl)camptothecin (30');

7-ethyl-10-ethyl camptothecin (31');

7-ethyl-10-(2-methoxycarbonyl-ethyl)camptothecin (32');

7-ethyl-10-(2-hydroxycarbonyl-ethyl)camptothecin (33');

7-ethyl-10-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (34');

7-ethyl-10-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin 35');

7-ethyl-10-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin 36');

7-ethyl-10-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (37');
7-ethyl-10-(3-oxo-butyl)camptothecin (38');
7-ethyl-10-(3-oxo-3-phenyl-propyl)camptothecin (39');
7-ethyl-10-(2-aminocarbonyl-ethyl)camptothecin (40');
11-ethyl camptothecin (41');
11-(2-methoxycarbonyl-ethyl)camptothecin (42');
11-(2-hydroxycarbonyl-ethyl)camptothecin (43');
11-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (44');
11-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (45');
11-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (46');
11-[(2-acetylamino-2-hydroxycarbonyl)-ethyl]camptothecin (47');
11-(3-oxo-butyl)camptothecin (48');
11-(3-oxo-3-phenyl-propyl)camptothecin (49');
11-(2-aminocarbonyl-ethyl)camptothecin (50');
9-amino-12-ethyl camptothecin (51');
9-amino-12-(2-methoxycarbonyl-ethyl)camptothecin (52');
9-amino-12-(2-hydroxycarbonyl-ethyl)camptothecin (53');
9-amino-12-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (54');
9-amino-12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin 55');
9-amino-12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin 56');
9-amino-12-[(2-acetylamino-2-hydroxycarbonyl)-ethyl] camptothecin (57');
9-amino-12-(3-oxo-butyl)camptothecin (58');
9-amino-12-(3-oxo-3-phenyl-propyl)camptothecin (59');
9-amino-12-(2-aminocarbonyl-ethyl)camptothecin (60');
10-amino-9-ethyl camptothecin (61');

10-amino-9-(2-methoxycarbonyl-ethyl)camptothecin (62');
10-amino-9-(2-hydroxycarbonyl-ethyl)camptothecin (63');
10-amino-9-[(2-acetylamino-2-methoxycarbonyl)-ethyl]
camptothecin (64');
10-amino-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin
(65');
10-amino-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin
(66');
10-amino-9-[(2-acetylamino-2-hydroxycarbony)-ethyl]
camptothecin (67');
10-amino-9-(3-oxo-butyl)camptothecin (68');
10-amino-9-(3-oxo-3-phenyl-3-one-propyl)camptothecin (69');
10-amino-9-(2-aminocarbonyl-ethyl)camptothecin (70');
12-ethyl camptothecin (71');
12-(2-methoxycarbonyl-ethyl)camptothecin (72');
12-(2-hydroxycarbonyl-ethyl)camptothecin (73');
12-[(2R,S,)(2-acetylamino-2-methoxycarbonyl)-
ethyl]camptothecin (74');
12-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (75');
12-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (76');
12-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (77');
12-(3-oxo-butyl)camptothecin (78');
12-(3-oxo-3-phenyl-propyl)camptothecin (79');
12-(2-aminocarbonyl-ethyl)camptothecin (80');
10-hydroxy-9-ethyl camptothecin (81');
10-hydroxy-9-(2-methoxycarbonyl-ethyl)camptothecin (82');
10-hydroxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (83');
10-hydroxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)
camptothecin (84');
10-hydroxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin
(85');

10-hydroxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (86');

10-hydroxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (87');

10-hydroxy-9-(3-oxo-butyl)camptothecin (88');

10-hydroxy-9-(3-oxo-3-phenyl-3-one-propyl)camptothecin (89');

10-hydroxy-9-(2-aminocarbonyl-ethyl)camptothecin (90');

10,11-methylendioxy-9-ethyl camptothecin (91');

10,11-methylendioxy-9-(2-methoxycarbonyl-ethyl)camptothecin (92');

10,11-methylendioxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (93');

10,11-methylendioxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl)camptothecin (94');

10,11-methylendioxy-9-[(2-amino-2-methoxycarbonyl]-ethyl) camptothecin (95');

10,11-methylendioxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl] camptothecin (96');

10,11-methylendioxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl]camptothecin (97');

10,11-methylendioxy-9-(3-oxo-butyl)camptothecin (98');

10,11-methylendioxy-9-(3-oxo-3-phenyl-propyl)camptothecin (99');

10,11-methylendioxy-9-(2-aminocarbonyl-ethyl)camptothecin (100');

10-methoxy-9-ethyl camptothecin (101');

10-methoxy-9-(2-methoxycarbonyl-ethyl)camptothecin (102');

10-methoxy-9-(2-hydroxycarbonyl-ethyl)camptothecin (103');

10-methoxy-9-[(2-acetylamino-2-methoxycarbonyl]-ethyl) camptothecin (104');

10-methoxy-9-[(2-amino-2-methoxycarbonyl]-ethyl)camptothecin (105');

10-methoxy-9-[(2-amino-2-hydroxycarbonyl)-ethyl]camptothecin (106');

10-methoxy-9-[(2-acetylamino-2-hydroxycarbony)-ethyl] camptothecin (107');

10-methoxy-9-(3-oxo-butyl)camptothecin (108');

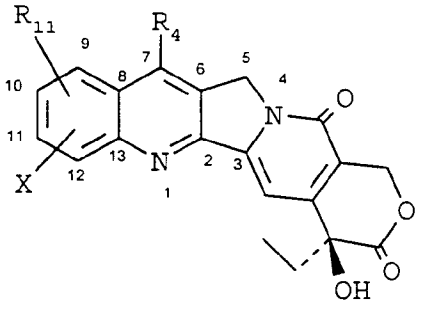
10-methoxy-9-(3-oxo-3-phenyl-propyl)camptothecin (109');

10-methoxy-9-(2-aminocarbonyl-ethyl)camptothecin (110');

and, where a salifiable substituent is present on the molecule framework, their pharmaceutically acceptable salts.

4. A process for preparing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, said process comprising

1) reacting a compound of formula (II)



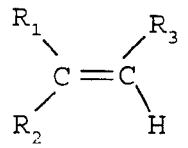
(II)

wherein

R_{11} is a halogen atom, $-OSO_2R_{12}$ wherein wherein R_{12} is C_1-C_5 alkyl unsubstituted or substituted at the terminal carbon atom by one, two or three halogen atoms or an optionally substituted phenyl ring;

R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; and

X is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_6 alkanoyloxy, benzoyloxy, amino hydroxy, nitro, halogen or it is a methylenedioxy group linked to the positions 10 and 11 of the molecule, with a compound of formula (III)



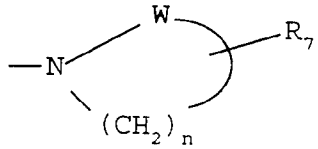
(III)

wherein

R_1, R_2 and R_3 are as defined under (a) or (b) below:

(a) R_1 and R_2 are each independently hydrogen; C_1-C_4 alkyl; C_3-C_7 cycloalkyl; phenyl C_1-C_6 alkyl; an optionally substituted phenyl ring;

$-NR_5R_6$ wherein one of R_5 and R_6 is hydrogen, C_1-C_6 alkyl or benzyl and the other is hydrogen C_1-C_6 alkanoyl, an optionally substituted benzoyl, phenyl C_1-C_6 alkanoyl, an optionally substituted C_1-C_6 alkoxycarbonyl, an optionally substituted phenoxycarbonyl or phenyl C_1-C_6 alkoxycarbonyl, or R_5 and R_6, combined together with the nitrogen atom to which they are linked, form a 4-7 membered saturated, optionally substituted, heteromonocyclic ring, represented by a group (G)



(G)

wherein W is -C=O, R_7 is hydrogen or C_1-C_6 alkyl and n is an integer of 2 to 5;

$COOR_8$ wherein R_8 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or phenyl C_1-C_6 alkyl; or

COR_9 wherein R_9 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl C_1-C_6 alkyl, an optionally substituted phenyl ring, $NR_{10}R_{11}$ wherein R_{10} and R_{11} are each independently hydrogen or C_1-C_6 alkyl; and

R_3 is hydrogen, C_1-C_6 alkyl or an optionally substituted phenyl; or

(b) R_1 and R_3, combined together, form a 5-8 membered, optionally substituted carbomonocyclic ring; and

R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_7 cycloalkyl;

so obtaining a compound of formula (I) wherein the symbol ---- represents a double bond;

and, if desired,

2) optionally reducing a compound of formula (I) (as obtained under step 1) into a corresponding compound of formula (I) wherein the symbol ---- represents a single bond, and/or if desired, salifying a compound of formula (I).

5. A pharmaceutical composition which comprises a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof as an active ingredient and a pharmaceutically acceptable carrier and/or diluent.

6. A compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof for use as an antitumor agent.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 96/02008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/22 A61K31/435 //(C07D491/22,311:00,221:00,221:00,209:00),(C07D491/22,317:00,311:00,221:00,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 325 247 (KABUSHIKI KAISHA YAKULT HONSHA) 26 July 1989 see page 8, line 51 - page 9, line 23; claims 1,15; example 16 ---	1,5
X	WO,A,91 04260 (RESEARCH TRIANGLE INSTITUTE) 4 April 1991 see claims 1,33; example 15 ---	1,5
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 1, 1991, WASHINGTON US, pages 98-107, XP002013003 W. D. KINGSBURY ET AL.: "Synthesis of water soluble (aminoalkyl)camptothecin analogues: inhibition of topoisomerase I and antitumor activity" see compounds 19 and 35 in tables I and II --- -/--	1,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 1996	13.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 110, no. 15, 1989 Columbus, Ohio, US; abstract no. 128163n, W. K. ENG ET AL.: "Evidence that DNA topoisomerase I is necessary for the cytotoxic effects of camptothecin" page 30; XP002013004 see abstract and 12 Coll. Index, Chem. Subst., p. 78043, c.3 (101-103) and p. 78044, c.1 (71-73) & MOL. PHARMACOL, vol. 36, no. 4, 1988, pages 755-760, -----	1,5

1

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Interna al Application No
PCT/EP 96/02008

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-325247	26-07-89	JP-A-	1186892	26-07-89
		JP-B-	6015547	02-03-94
		CA-A-	1332414	11-10-94
		DE-T-	68906552	16-12-93
		ES-T-	2056962	16-10-94
		US-A-	5061800	29-10-91
WO-A-9104260	04-04-91	AU-B-	640950	09-09-93
		US-A-	5180722	19-01-93